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Effect of indacaterol on arterial blood gases in patients suffering from acute exacerbation of COPD

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Summary
Aim: The administration of β_2-agonists to patients with airways obstruction often results in transient decrease in PaO_2 despite concomitant bronchodilation. This effect is potentially dangerous for patients suffering from acute exacerbation of COPD (AECOPD). In this study, we investigated the effect of indacaterol 150 μg and 300 μg on the arterial blood gas tensions of hospitalised patients with AECOPD.
Methods: We explored the acute effects on arterial blood gases and spirometry of two doses of indacaterol Breezhaler (150 and 300 μg) in 12 patients hospitalised because of an AECOPD in 2 non-consecutive days under open-label, randomized, crossover conditions, with blind evaluation. Blood specimens were taken just before the inhalation and at 15, 30, 60, 120, 240 and 360 min after inhalation of each treatment, and spirometry was performed at the same time points.
Results: Both doses of indacaterol did not cause significant changes in blood gases, although some patients with relatively well-preserved PaO_2 presented transient episodes of oxygen desaturation that normalize spontaneously in a very short time. Moreover, they induced a significant mean increase in FEV_1 and FVC, although the improvement caused by indacaterol 300 μg was larger.
Conclusions: Indacaterol up to 300 μg is a potent bronchodilator that may induce small, transient decrease in PaO_2 mainly in patients with relatively well-preserved PaO_2. There appeared to be no clinical consequences of these PaO_2 abnormalities in patients suffering from AECOPD.

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Introduction

Short-acting inhaled β_2-agonists (SABAs) such as salbutamol and terbutaline are usually the preferred bronchodilators for treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) [1]. Actually, some studies suggest that these agents, as a class, are of benefit in AECOPD, showing improvements in lung function and dyspnoea scores [2]. However, there is a great deal of controversy regarding the timing and optimal dose of SABAs, also considering that the duration of the bronchodilator effect of SABAs is decreased in AECOPD [3]. For this reason, several authors suggest not only using larger-than-usual doses that are sometimes necessary to relieve airway obstruction, but also to shorten the posologic interval [2,4].

The use of long-acting, inhaled β_2-agonists (LABAs) formoterol and salmeterol should be another potential option to overcome the reduced functional half-life of SABAs in AECOPD, although they are still not approved for use in this pathologic condition [5]. This assumption is supported by results of small studies suggesting a potential use of LABAs during AECOPD [6–9]. This is particularly true for formoterol because of its rapid onset and long duration of action.

Indacaterol is the first once-daily LABA approved as a maintenance bronchodilator treatment of airflow obstruction in adult patients with COPD [10,11]. Single doses of indacaterol 150 and 300 μg demonstrate a fast onset of action similar to that for salbutamol [12]. The rapid onset of action, duration of bronchodilation for at least 24 h, and an optimal safety profile make this drug an interesting therapeutic option in AECOPD, although indacaterol has be approved only for the treatment of stable COPD. However, no study has yet assessed the impact of this once-daily LABA on partial pressure of oxygen in arterial blood (PaO_2).

This is a potential limitation to the use of indacaterol in AECOPD because the administration of β_2-agonists to patients with airways obstruction often results in a transient decrease in PaO_2 despite concomitant bronchodilation [13], although hypoxaemia induced by β_2-agonists is usually mild, at least in stable COPD [14,15]. Nonetheless, this effect could be potentially dangerous for patients suffering from AECOPD. In fact, AECOPD are frequently associated with deterioration in gas exchange and hypoxaemia. Increased inequality in ventilation–perfusion (V_A/Q) relationships appears to be the major determinant of these changes [16].

In stable COPD we already observed that the inhalation of indacaterol 150 μg induced a modest but significant decrease in blood oxygen saturation (SpO_2) up to 60 min and a second dose of indacaterol 150 μg significantly decreased the SpO_2 mean value up to 360 min [17]. Since the decrease in SpO_2 could be potentially dangerous for patients suffering from AECOPD and hypoxaemia, we aimed to investigate the acute effects of indacaterol inhalation on the arterial blood gas tensions of hospitalized patients with AECOPD.

Patients and methods

Study population

Twelve Caucasian patients admitted to our Unit were recruited on the basis of having an AECOPD requiring hospitalization. The presence of an AECOPD was diagnosed when physician observed a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD [18]. Exacerbations were considered severe because patient/physician recognised obvious and/or rapid deterioration in condition, requiring hospitalisation [18]. Because of the severity of the exacerbation, all patients, who had been transferred to our Unit from the Emergency Room when they were improved but still needed a period of monitoring before discharge, had an arterial catheter placed in the brachial artery during their stay in the Emergency Room to facilitate monitoring of arterial blood gases. Arterial catheterization is used normally in the management of critically ill patients, both for continuous blood pressure monitoring and access to the arterial circulation to obtain frequent blood gas measurements [19]. The exclusion criteria were: personal or family history of asthma, atopy, allergic disease, presence of eosinophilia, use of systemic steroids within the preceding month, presence of severe hypertension, or uncontrolled (or difficult to control) diabetes mellitus, or if a specific cause for the exacerbation, such as pneumonia, pneumothorax, or heart failure, was diagnosed. Patients were also excluded if they were at risk of imminent acute respiratory failure requiring mechanical ventilation or admission to the intensive care unit ($pH < 7.30$ and/or $PaCO_2 > 70$ mmHg, and/or $PaO_2 < 50$ mmHg despite supplemental oxygen). None of the patients was β_2-agonist-naïve. The ethics committee approved the study and all patients gave written informed consent. Table 1 illustrates the characteristics of the enrolled patients.

Study protocol

The study was designed as a single centre open-label, randomized, crossover conditions, with blind evaluation study. It started in each patient two days after admission in our Unit, when we had been able to confirm the substantial improvement of the episode of AECOPD but we were still feeling the need to monitor the patient's blood gas status, after a stay in emergency room fluctuating from three to 6 days.

All patients received indacaterol Breezhaler 150 μg (1 inhalation) + placebo (1 inhalation) or indacaterol Breezhaler 300 μg (2 inhalations) in two days, separated from one another by 48 h in order to reduce the carry-over effect of indacaterol.

Oral bronchodilators were not permitted during the study. SABAs were permitted soon after each test when required. Due to ethical considerations, all patients were treated with oral prednisolone 30-mg daily and supplemental oxygen, when required, soon after the end of each session. All patients also received a treatment with an antibiotic (ciprofloxacin, clarithromycin or ceftriaxone). Patients were asked not to consume cola drinks, coffee or tea and not to smoke in the hours before and during the investigation.

After a rest of 15 min and before the inhalation of indacaterol, while the patient was breathing room air and were seated in an armchair, samples of arterial blood (5 ml) were removed for measurement of PaO_2, $PaCO_2$, and pH

Table 1 The baseline characteristics of the randomised patients.

Patients	Gender	Age (yrs)	Height (cm)	Weight (kg)	BMI	Smoke (pack/y)	FEV_1 % Pred	FVC % Pred	PaO_2/FiO_2	A—a gradient (normal)
1	M	62	162	68	25.0	50	38.6	68.4	257	1.98 (19.5)
2	M	78	170	80	27.7	Ex 50	23.4	44.1	243	21.23 (23.5)
3	F	73	137	36	19.6	50	67.4	85.6	329	15.73 (22.25)
4	F	79	162	58	22.1	40	23.6	39.5	295	1.48 (23.75)
5	F	79	152	40	17.3	Ex 60	39.9	61.5	290	36.23 (23.75)
6	F	81	168	64	23.9	Ex 40	64.7	95.9	343	20.23 (24.25)
7	M	71	167	65	23.3	70	23.4	50.0	348	14.37 (21.75)
8	M	73	170	65	22.5	80	22.3	60.9	305	26.98 (22.25)
9	M	78	160	65	23.8	110	36.6	54.7	343	20.23 (23.5)
10	F	75	162	67	25.5	Ex 50	26.6	67.8	243	34.48 (22.75)
11	M	72	173	55	18.2	Ex 70	38.8	72.4	348	27.98 (22)
12	M	54	158	78	25.7	28	46.4	78.3	267	42.48 (17.5)

with a blood gas analyser. The machine output was checked daily with a standard test sample. Measurements were performed before (at least 6 h after the last doses of short-acting bronchodilators and corticosteroids) and 15, 30, 60, 120, 240 and 360 min after the administration of the drug, always on room air. Spirometry was performed at the same time intervals.

The change in PaO_2 after each treatment, from the baseline obtained on that day, was the primary outcome variable. The magnitude of changes in blood-gas tensions and spirometric values at each analysis time was compared among treatments. The paired *t*-test and analysis of variance (ANOVA) were used to determine the significance of differences among agents. Statistical significance was accepted at $P < 0.05$.

Results

Both doses of indacaterol induced a significant mean increase in FEV_1 and FVC, but the improvement caused by indacaterol 300 μg was larger (Fig. 1), although in some patients both doses were unable to induce any significant changes in FEV_1 (Fig. 2).

The inhalation of both doses of indacaterol did not induce significant changes in mean PaO_2 values (Fig. 1). However, the mean peak decrease in PaO_2 over the 6 h was −5.9 mmHg (95% CI: −1.4 to −10.4) after indacaterol 150 μg and −6.2 mmHg (95% CI: −2.7 to −9.8) after indacaterol 300 μg, respectively. Individual changes in PaO_2 showed that after inhaling indacaterol 150 μg, one patient presented a decrease of 23 mmHg at 60 min, another a

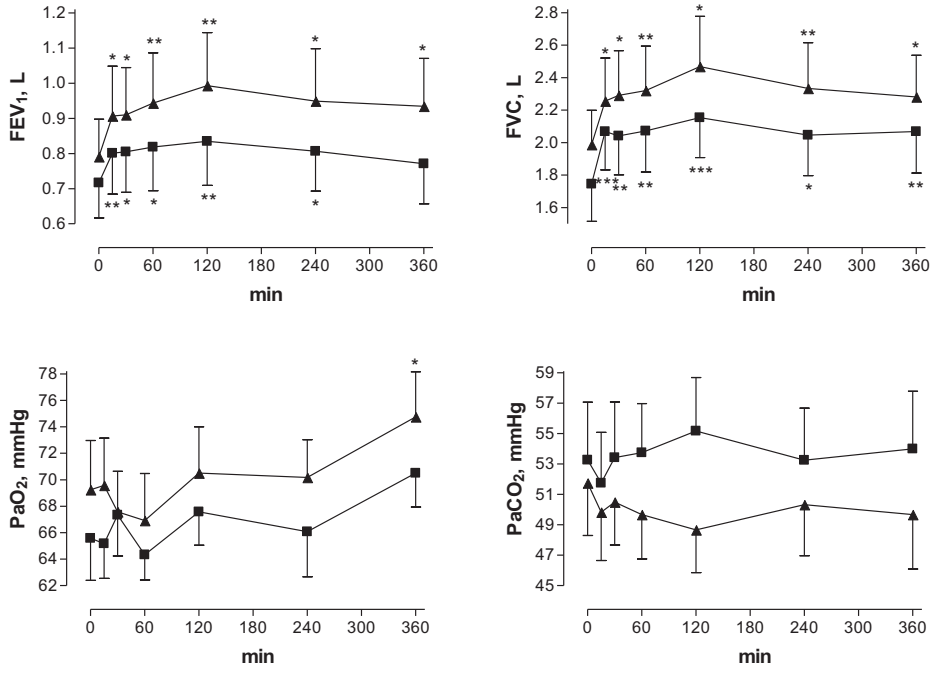

Figure 1 Mean changes (±se) in FEV_1, FVC, PaO_2, and $PaCO_2$ over time after administration of indacaterol 150 μg (squares) and 300 μg (triangles) via Breezhaler. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs. baseline.

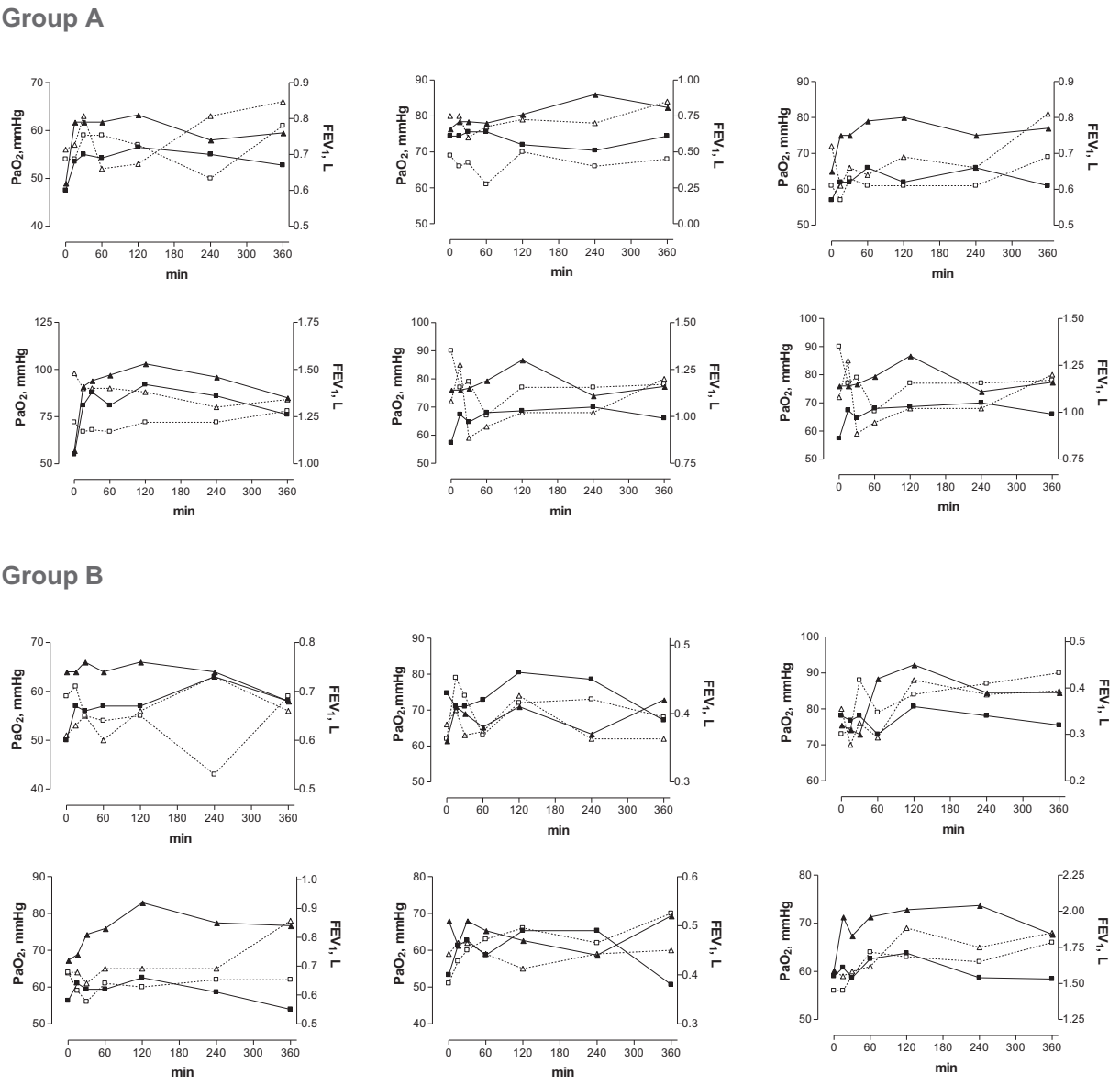

Figure 2 Individual changes in FEV_1 (solid line) and PaO_2 (dashed line) over time after administration of indacaterol 150 μg (squares) and 300 μg (triangles) via Breezhaler. Group A received first indacaterol 150 μg and then indacaterol 300 μg; Group B received first indacaterol 300 μg and then indacaterol 150 μg.

decrease of 16 mmHg at 240 min and two other subjects a decrease of 8 mmHg at 60 min and 30 min, respectively (Fig. 2). After the inhalation of indacaterol 300 μg, one patient showed a decrease in PaO_2 of 18 mmHg at 240 min, another of 13 mmHg at 30 min, a third of 11 Hg after 15 min and a fourth of 10 Hg at 15 min (Fig. 2). The decreases in PaO_2 were mainly observed in the patients with the highest basal PaO_2. In any case, all values returned to normal spontaneously. At 360 min, the mean value of PaO_2 was greater than baseline, with a statistically significant difference after indacaterol 300 μg (Fig. 1). Both indacaterol 150 and 300 μg induced a small and not significant mean decrease in $PaCO_2$ (Fig. 1). No patient showed a rise in $PaCO_2$.

Only indacaterol 150 μg significantly increased the alveolar-arterial oxygen (A—a) gradient at 15 min (Fig. 3). It should be noted that in patients with an A—a gradient higher than normal at baseline, both doses of indacaterol did not induce any significant increase in this parameter as opposed to what was observed in subjects with a normal A—a gradient at baseline (Fig. 3). However, the observed increases were always within the normal values.

We were unable to find a linear relationship between the greatest changes in FEV_1 and peak decreases in PaO_2 with both doses of indacaterol (Fig. 4).

Discussion

The results of this pilot study, which is the first to best of our knowledge that has explored the effect of indacaterol on arterial blood gases and, consequently, must be

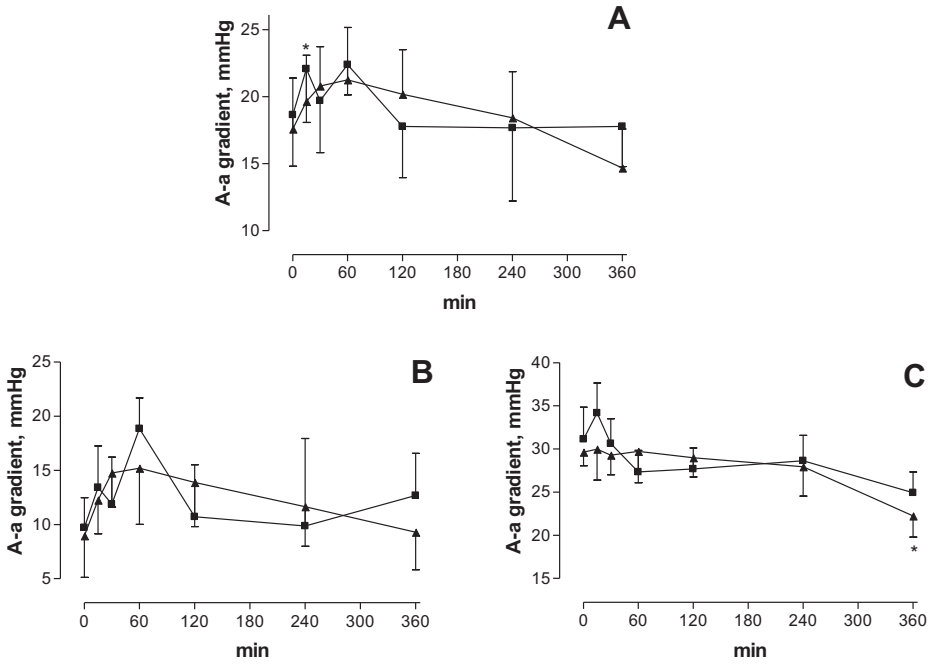

Figure 3 Mean changes (±se) in A—a gradient over time after administration of indacaterol 150 μg (squares) and 300 μg (triangles) via Breezhaler (A, all patients; B, patients with a normal basal A—a gradient; C, patients with a high basal A—a gradient). *$P < 0.05$ vs. baseline.

considered a preliminary note, suggest two important points related to the use of this once-daily LABA.

First of all, despite being a long-acting bronchodilator with high affinity for β_2-adrenoceptors, indacaterol does not seem to cause any significant change in blood gases even in AECOPD, although some patients can present transient episodes of oxygen desaturation that normalize spontaneously in a very short time. In any case, we observed a decrease in PaO_2 mainly in patients with relatively well-preserved PaO_2. This is an important confirmatory finding. It has already been documented that β-agonists cause an increase in V_A/Q inequality in patients having PaO_2 values greater than 60 mmHg which results in a moderate fall in the PaO_2, whereas in patients with PaO_2 values less than 60 mmHg, no significant changes in V_A/Q distributions or PaO_2 after β-agonists has been observed [20]. Reasons for this are undoubtedly complex but may involve loss of hypoxic pulmonary vasoconstriction due to morphologic changes of the pulmonary vasculature [20]. It has been suggested that, in more severe COPD with more prominent hypoxaemia, the pulmonary vascular tone is more disturbed than in patients with less severe disease, with the vessels more rigid and fixed, hence less liable to be vasodilated by β-agonists [21].

The second main observation is that when the obstruction is very tight, it may be necessary to use a higher indacaterol dose than that commonly prescribed for a COPD patient who is in a stable clinical condition. This does not seem to be a problem if we focus on the impact of indacaterol on blood gas levels because our data seem to rule out that the increase in dose of a β_2-agonist may aggravate the PaO_2 response, in contrast to what was originally thought by Ferrer and co-workers [22]. In any case, we already documented that the administration of indacaterol 300 μg to patients admitted to emergency department for an AECOPD resulted in a greater improvement of pulmonary function compared with traditional therapy, with a statistically significant improvement in PaO_2 [23].

The transient decrease in PaO_2 induced by inhaled β_2-agonists despite concomitant bronchodilation has been attributed to the pulmonary vasodilator action of these agents, increasing blood flow to poorly ventilated lung regions resulting in greater V_A/Q inequalities [21]. The outcome of V_A/Q mismatch is admixture of venous blood to oxygenated blood leading to a decrease in PaO_2, the arterial saturation of haemoglobin with oxygen, and thereby the arterial oxygen content that reaches the left-sided circulation [24]. However, although LABAs have an acute vasodilator action in the airways, the modest contribution of bronchial circulation to the lung's blood flow indicates that it does not participate significantly in gas exchange and suggests that the impact of the vasodilating effect of β_2-agonists on V/Q inequality is small and unimportant [25].

Multiple effects in different compartments involved in gas exchange (including airflow and blood flow distribution) can cause a decrease in PaO_2 [24]. Alterations that affect the post-alveolar (capillary) side, for example, a change of the central venous oxygen saturation of haemoglobin due to an alteration in cardiac output, changes in ventilation or acute bronchial obstruction can affect PaO_2 and therefore need to be taken into consideration [25]. Unfortunately, these constructs were not verified in the present study, which was only focused on the impact of indacaterol on arterial blood gases and the possible link between bronchodilation and decrease in PaO_2. What, however, this study allows to exclude is that there is a dose-dependent effect of indacaterol on arterial blood gases. Furthermore, bronchodilation is completely independent of this systemic effect.

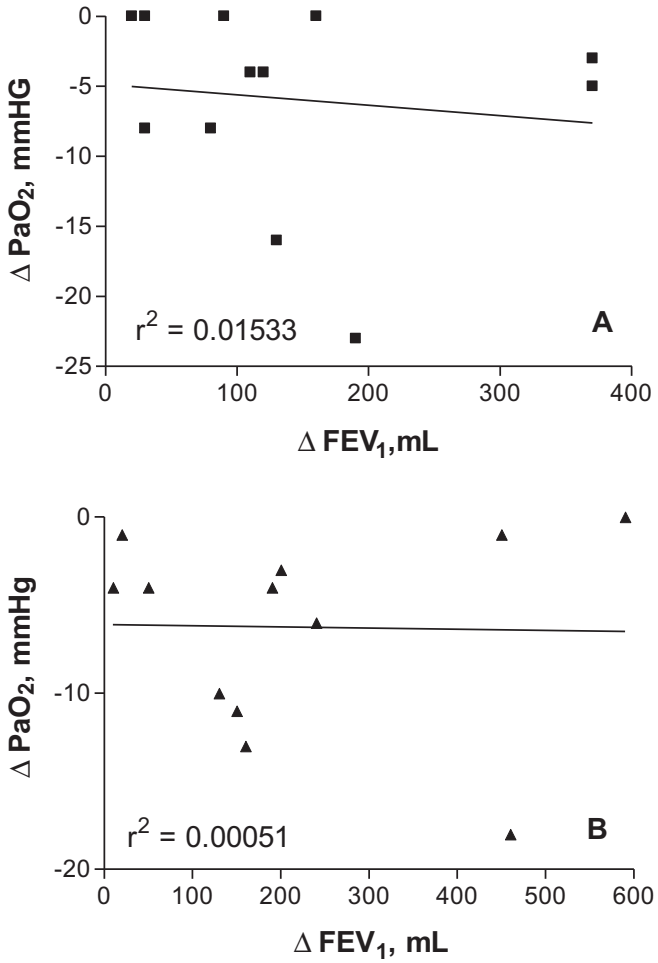

Figure 4 Relationship between the greatest changes in FEV_1 and peak decreases in PaO_2 with indacaterol 150 μg (A) and 300 μg (B) via Breezhaler.

Karpel co-workers [4] reported that metaproterenol produced a mean decline in PaO_2 of 6.2 mmHg during AECOPD. Nonetheless, the small effect of indacaterol on blood gases of our patients with AECOPD fits rather well with the observation of Polverino and co-workers [21], who showed that the administration of 5.0 mg salbutamol at the time of exacerbation did not aggravate the already compromised pulmonary gas exchange. A weaker (or even absent) hypoxic pulmonary vascular response related more to acutely severe alveolar hypoxia than to a permanent structural derangement of the pulmonary vasculature was suggested a the most likely explanation of the lack of gas exchange response to salbutamol in AECOPD [21]. However, also other explanations were postulate [26]. For example, β_2-agonists can minimize the subsequent release of other inflammatory mediators into the pulmonary circulation, with vasodilator effects during AECOPD that can disturb the underlying V/Q imbalance [26]. Moreover, the potential of β_2-agonist-induced inhibitory effects on the postcapillary bronchial venoconstriction and airway microvascular leakage, possibly amplified by their potent relaxant effect on conducting airways, cannot be overlooked [26].

Whatever the mechanisms behind the changes in arterial blood gases, our findings were broadly reassuring. They indicated that indacaterol up to 300 μg is a potent bronchodilator that may induce small, transient decrease in PaO_2 mainly in patients with relatively well-preserved PaO_2 and, consequently, there appeared to be no clinical consequences of these PaO_2 abnormalities. Moreover, our study suggests that an increase in $PaCO_2$ following a high dose of indacaterol is uncommon in patients with AECOPD.

However, since all our patients were taking inhaled β_2-agonists regularly prior to be studied, and it is well-known that regular use of these agents can lead to down-regulation of their systemic response [13], it is now mandatory to repeat the study in β_2-agonist-naïve subjects. Moreover, since Polverino and co-workers [21] documented that while in convalescence, the gas exchange response to an inhaled β_2-agonist is deleterious resulting in small decrements in PaO_2 due to V/Q worsening, the study must be repeated in patients suffering from stable COPD.

Conflict of interest statement

We declare that we have no conflict of interest with this study that has not been sponsored by any Drug Company. However, Mario Cazzola is a member of a scientific advisory board and the speaker bureau of Novartis and is a consultant of Chiesi Farmaceutici.

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